



Ottawa Hull K1A 0C9

(21)	(A1)	2,135,669
(22)		1994/11/10
(43)		1996/05/11

(51) Int.Cl. ⁵ A61K 31/70

(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Ribavirin as Hepato (Liver) Protecting Agent

(72) Johannesson, Nils O. - U.S.A. ;
Gait, John E. - U.S.A. ;
Kosutic, Gordana - U.S.A. ;

(71) ICN Pharmaceuticals, Inc. - U.S.A. ;

(57) 17 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.



2135669

ABSTRACT

Use of Ribavirin as a hepato (liver) protecting agent.

TITLE OF INVENTION**RIBAVIRIN AS HEPATO (LIVER) PROTECTING AGENT**

This invention relates to new uses for Ribavirin, novel uses of Ribavirin for the treatment of chronic hepatitis C, novel methods for treating hepatitis C, and new dosages suitable for use when treating hepatitis C.

Ribavirin was taught in both United States Patents 3,798,209, 3,927,216, and 4,211,771 teaches the processes for treating viral diseases in humans which comprises administering to human patients an antiviral agent which has as its active component the compound Ribavirin. Canadian Patent 1,261,265 relates to formulations and the manufacture of formulations for the medical treatment of viral diseases in humans which are caused by, among other viruses, Arboviruses which included hepatitis C. The formulations taught in that patent comprise an effective non-toxic amount of a composition containing from .01% to 50% by weight of the total weight of the composition of a compound Ribavirin.

In "Pilot study of Ribavirin Therapy for Chronic Hepatitis C" accepted for publication April 28, 1992 in *Hepatology* at page 649, the article discussed the treatment of a small number of patients with chronic hepatitis C using Ribavirin. In the pilot study itself, Ribavirin was given for six months in doses that increased at two-month intervals from 600 mg to 1,000 mg to 1,200 mg per day. The serum alanine aminotransferase (ALT) levels gradually decreased in all 13 treated patients. In the three to six month period after cessation of Ribavirin therapy, serum aminotransferase activities gradually rose to near pre-treatment levels in all but one patient. No significant improvement was seen in liver histological appearance. The article went on to say that these findings suggest that Ribavirin has a beneficial effect in patients with chronic hepatitis C.

Another article entitled "Ribavirin Treatment for Chronic Hepatitis C" published in *Lancet*,; 1991 (May 4); volume 337: at pages 1058

to 1061, discussed the treatment of ten patients in a pilot study, all of whom had biopsy-proven chronic non-A, non-B hepatitis and were repeatedly positive for antibodies to hepatitis C virus. The treatment was with oral Ribavirin, 1,000 to 1,200 mg per day in two divided doses for twelve weeks. Once again, serum ALT levels fell when treated. However, within six weeks of the end of treatment, the median serum alanine aminotransferase concentration was not significantly different from that before treatment.

In *Hepatology*, 1993; volume 18, number 4, pt. 2, a summary entitled "Randomized, Double-Blind Placebo-Controlled Trial of Ribavirin Therapy for Chronic Hepatitis C" is provided wherein 58 patients with chronic hepatitis C entered a randomized, double-blind controlled trial of Ribavirin (600 mg BID orally for twelve months) versus placebo. As in the previous studies, serum ALT values fell, but rose after the cessation of therapy in all but two of four responders. The conclusion from the trial was that prolonged Ribavirin therapy was associated with significant improvement in serum ALT levels (despite unchanged serum HCV RNA levels) and hepatic lobular mucosis.

The prior patents and articles referred to do not lead the reader to the appreciation that the Ribavirin reduce serum ALT levels in some patients to normal levels where they remain for a prolonged period of time after the suspension of treatment with Ribavirin. Further, there is no appreciation of the ability to treat a patient for a prolonged period of time with Ribavirin, and that as a result of that treatment the serum ALT levels remain normal even after cessation of treatment. Furthermore, there is no teaching that the use of Ribavirin may protect the liver, acting as a hepatoprotecting agent, thus at least preventing worsening of the condition of the patient's liver, and, in many cases, improving the condition of the patient's liver.

In treating chronic hepatitis C with the antiviral agent Ribavirin, it would also have been expected by persons skilled in the art that the level of

hepatitis C virus would diminish in the liver because Ribavirin is identified as an antiviral agent. This is surprisingly not the case, however, even though the serum ALT levels reduced.

In the Ribavirin studies carried out in accordance with this invention, the primary response parameter was reduction in serum ALT levels. Elevation of ALT indicates biochemical evidence of hepatic inflammation, and reduction of the ALT level is an accepted response criterion in clinical studies of therapeutic agents in hepatitis C. In all of the studies in the Ribavirin clinical program, phase II and phase III Ribavirin was significantly superior to placebo in normalizing and reducing ALT levels during treatment. Using the integrated definition of ALT response, which includes normalization of ALT at the end of treatment and a clinically meaningful definition of partial response, 46% of Ribavirin-treated patients were responders compared to 4% of placebo controls ($p < 0.001$). Following withdrawal of Ribavirin, the ALT levels of the majority of responders reverted to baseline levels. However 12% of the patients did maintain the ALT response throughout the follow-up period, and we have discovered that there is a correlation between the rate of sustained response and duration of treatment. The rate of sustained response was greater in the study of the longest duration (i.e., 48 weeks) and we expect even a greater sustained response after longer treatment. According to our invention, the effect of treatment on liver histology was assessed in the same manner in each of the phase III studies. The Knodell scoring system was strictly adhered to throughout. For each patient the effect of treatment was determined by the change in score from baseline to the end of therapy. All liver biopsy assessments (taken before and after treatment) were performed in a blinded fashion, by a single pathologist in each of two studies (92-001 and CT00/002), or, in the case of another study (91-DK-178), by two pathologists who agreed on each specimen. In each study, analysis of Knodell scores by the methods specified in the analysis plans did not reveal a statistically significant

difference between the treatment groups. In each study, however, there is a consistent numerical trend in favour of Ribavirin in the changes in total scores and in many of the component scores. This same trend is thus apparent when the data from the three studies is combined. The methods of collection of the liver biopsy data described above justify combining the data in this way. It is of interest that the trend applies not only to improvement of scores but also to worsening, indicating that even if no patients in either treatment group improve, then fewer patients in the Ribavirin group are worsening. This is an important observation considering that one objective of treatment is to prevent deterioration of a chronic and progressive condition. Analysis of the combined data by analysis of covariance using baseline Knodell score as covariate reveals statistically significant differences in favour of Ribavirin for the total Knodell score and for each of the four subscores. This analysis takes into account the baseline variability in Knodell scores, and the tendency for baseline scores at the extremes of the scale to regress to the mean without any treatment effect.

The mean changes in the scores for Ribavirin-treated patients are only small, but due to small variances the differences from placebo are statistically significant. It is of interest to note that the only Knodell sub-score that does not improve is fibrosis, and that there is less deterioration in the Ribavirin group than in the placebo group.

Within the Ribavirin group, comparison of ALT responders and non-responders revealed that ALT responders experienced a significantly greater improvement in liver histology as compared to ALT non-responders. The mean fall in total Knodell score was approximately two points for ALT responders as compared to one point for all Ribavirin-treated patients. A fall in total Knodell score of two points is generally considered by hepatologists to be clinically significant. There was thus a statistically significant positive correlation between ALT response and a clinically significant degree of improvement in liver histology. This is an important finding, as

measurement of ALT levels is an accepted, non-invasive method of monitoring the degree of hepatic inflammation, while improvement of liver histology, or at least prevention of further deterioration, is the ultimate clinical objective.

Regarding reduction and elimination of HCV-RNA, response rates were generally low in all of the phase II and phase III studies, with no significant differences between Ribavirin and placebo (or any evidence of a trend in favour of Ribavirin). This was an unexpected result, especially considering the positive effects of Ribavirin therapy on ALT reduction and the finding herein of the improvement in liver histology. Higher rates of HCV-RNA elimination have been reported during interferon therapy of hepatitis C, but following withdrawal of therapy the great majority of patients eventually become HCV-RNA positive again. It is not known how elimination of HCV-RNA relates to improvement in liver histology, which is the ultimate clinical objective. Until recently it has been generally accepted that the primary objective should be eradication of viremia, the assumption being that clinical benefit cannot be expected if viremia persists. The efficacy of Ribavirin against the biochemical and histological parameters of hepatic inflammation without an accompanying reduction of viremia we found changes this assumption. While the eradication of viremia would appear to be a logical objective of treatment, we have found that such eradication is clearly not a prerequisite for clinical improvement in all patients. As the hepatitis C virus, like other RNA viruses, does not exist as a single entity but as a mixture of sub-species, it is, we believe, that Ribavirin inhibits the most pathogenic subpopulation of viruses while leaving other populations relatively unaffected. The liver cell and cells and, thus, the liver is thus protected against the chronic pro-inflammatory effect of viremia. Also, the practicality of eradication of viremia as the primary objective of treatment can now be considered in light of our discovery and developments.

While interferon can be effective in the short term, this agent is not suitable for the long term maintenance therapy required to prevent relapse, due to poor tolerability, some serious adverse reactions and the unacceptability of long term injection therapy. Thus long-term control of the hepatitis C disease process and prevention of liver damage should be the primary objective of treatment, at least in those patients in whom attempts to eradicate viremia have failed. Due to its oral administration and good tolerability Ribavirin is a suitable agent for the long-term amelioration of the effects of chronic hepatitis C infection on the liver (beyond a year). As we have found positive correlation between ALT reduction and improvement in liver histology, routine monitoring of the response to treatment is simple and non-invasive. These same properties facilitate the introduction of active treatment at an earlier stage of disease, the objective being to prevent the progression of even minimal liver damage.

In the phase III clinical program, the efficacy of Ribavirin in terms of reducing ALT levels appeared to be dose-related. In one study (CT00/002) dose was determined at baseline according to weight, and in all studies the variation in patients' weight, permitted discrimination between patients on the basis of the daily dose calculated as mg per kg. It was thus possible to perform an analysis of dose response. Guidance for the choice of the standard daily dose of Ribavirin for the phase III studies (1200mg) was provided by the results of the phase II study (90-DK-49), in which the dose varied from 600 mg to 1200 mg according to efficacy and tolerability (with no adjustment by patient weight). This study was small but indicated that efficacy in reducing ALT levels was dose-related within the dose range employed in the study, while the high dose was as well tolerated as the low dose. We have discovered that the pharmacokinetics of Ribavirin are linear over the dose range 600-2400 mg/day.

The effect of Ribavirin on symptoms of hepatitis was assessed in two of the phase III studies. In one study (92-001), Ribavirin improved fatigue

in comparison to placebo. There were no significant differences for other symptoms. In another study (91-DK-178), Ribavirin did not differ from placebo in the effect on symptoms.

There was no apparent effect of age, but females had a higher response rate than males (60% versus 40%, $p=0.046$). We determined this was in fact a dose effect, due to the lower weights of females. Regarding baseline characteristics, there were trends towards lower response rates in patients with the highest baseline ALT levels and total Knodell scores because we believe these patients probably had more severe disease in the first place. There was no apparent effect of duration of hepatitis or previous exposure to interferon on ALT response.

Furthermore, there is no evidence we have found of loss of ALT response with increasing duration of treatment. Therefore, we predict on the basis of our tests that treatment can be carried out indefinitely to protect the liver.

We have therefore found that Ribavirin in the treatment of hepatitis C is, according to one important aspect of our invention, a hepato-protecting agent, which acts to protect the liver even if the Ribavirin is unable to eradicate or eliminate the virus from the liver. The liver is protected. As a result, because Ribavirin is well tolerated and can be taken for a substantial period of time (for example, for years), the applicants have discovered that the treatment of hepatitis C, and, in one embodiment, chronic hepatitis C, would involve the administration of an effective hepato protecting amount of Ribavirin to the patient (for example, 1200 mg of Ribavirin in a suitable oral dosage form per day) for a substantial period (for example, for in excess of 12 months). For the protection of the liver, other dosage amounts can be given according to our invention. The tests have found the above amounts well-tolerated and successful, and the duration of treatment appropriate. The dosage forms themselves may comprise the known 200 mg capsules [containing 200 mg Ribavirin, 50 mg Avicel, 46 mg Lactose, and 4 mg

Magnesium Stearate in a #1 shell 21 mm long by 7 1/2 mm in width] taken three at a time twice a day, or better still two, according to our invention two at a time, a total of 300 mg capsules taken (for a total of 12 mg) twice daily for 1200 mg per day, three 400 mg capsules each taken three times daily (for a total of 1200 mg), or two 600 mg capsules taken twice daily all for better patient compliance. Patients, after taking three 200 mg capsules twice daily for months tire of taking medication. Patients compliance becomes more difficult. Furthermore, it is important not to make the larger dosage sizes too large so that the patient is uncomfortable taking the medication. Furthermore, immediate release formulations are desired with preferably large amounts of Ribavirin being included in each formulation relative to the total weight of the formulation, for example, greater than 70% of the formulation by weight (excluding the weight of any covering, for example, capsule shell) being Ribavirin with the maximum amount of about less than 80% by weight of the formulation. In a number of formulations, they may be manufactured according to aspects of embodiments of our invention as follows:

STRENGTH OF CAPSULE:	300 mg	400 mg	600 mg
COMPOSITION:			
(a) Ribavirin - active medicine	300 mg	400 mg	600 mg
(b) Diluent, for example: Avicel - a type of cellulose for diluting the active	75 mg	100 mg	150 mg
(c) Filler and Diluent, Lactose	29 mg	62 mg	63 mg
(d) Dispersant - Magnesium Stearate - dispersant, Lubricant	6 mg	8 mg	12 mg

Fill Wt.	410 mg	570 mg	825 mg
Shell Size for Capsule:	#0	#00	#000
Length	23 mm	25 mm	28 mm
Width	8 mm	9 mm	10 mm

Ribavirin (Virazole™) 300 mg, 400 mg & 600 mg Capsules: theoretical, immediate release formula.

Benefits: patient compliance - both sizes and amounts, for example:

300 mg: 2 capsules in the morning, 2 capsules in the evening 400 mg:

one capsule three times a day 600 mg: one capsule twice a day

For assisting doctors or patients with patient compliance, the capsules may be put on a strip and provided in seven-day dosage amounts on, for example, tear strips (blister packages) from which individual doses (for example) may be removed one at a time, so that the patient knows whether or not he/she has taken the appropriate dosage that day. In this regard, see Figures 1 to 6 which are discussed hereinafter. The material shown in the strips are blister packs in which one capsule is located in each blister. Each strip is perforated so that one capsule can be removed at one time from the strip. The packaging components used for manufacturing, for example, the four strips of six capsules per strip (totalling 24 capsules shown in Figure 2) may consist of a polyvinyl chloride blister, with a punch out foil backing. The finished package will be four strips of six capsules per strip or 24 capsules. Each blister may be made with the following material: the blister material may be Genotherm 1001 C Natural; Foil Backing may be a thin aluminium foil with an outside lacquer of polyester and an inside lacquer of VCVDC (vinyl chloride vinylidenechloride (copolymer)). The strips may be packed in a carton which may be a pre-printed chip-board carton to enclose the four strips of blister capsules.

Additionally, the strips can be provided in specified daily amounts, for example, a four day amount which a doctor may give to a patient for testing over a four-day period to help determine whether or not the patient is sensitive to Ribavirin and is able to take the desired dosage amount of Ribavirin. For example, a four-day test strip may amount to twenty-four 200 mg capsules provided in a blister pack which is handed to the

patient thereby providing a dosage amount of six capsules in four rows, three capsules taken at each dosage administration, giving 600 mg twice daily for four days. The blister package strips of Ribavirin may also constitute a week supply, two weeks supply, etc. to ensure patient compliance. In this way the patient is easily able to comply knowing what strip should be removed from what row as rows may be numbered and removing the appropriate amount at each dosage time.

The analyses of safety indicate that Ribavirin is a well-tolerated therapy. This low toxicity profile is demonstrated through analyses of the clinical studies in the treatment of hepatitis C as well as through review of individual study reports and review of published literature. No patients died during Ribavirin therapy; one patient died in the follow-up phase due to a condition which pre-dated exposure to Ribavirin. Out of 159 patients with chronic hepatitis C exposed to Ribavirin for periods ranging from 12-48 weeks, only 5 (3%) were withdrawn due to adverse events. Apart from one patient who developed anemia, none of the serious adverse events or withdrawals appeared to be related to Ribavirin. There was no pattern in the events occurring in these patients, and the events could not be explained by any known pharmacological effects of Ribavirin.

The most common side effect of Ribavirin is a mild, reversible hemolytic anemia which occurs in a substantial proportion of patients treated. This anemia can be a serious event in patients with impaired renal function, but in the great majority of patients with normal renal function it is a benign, self-limiting condition which is often asymptomatic, and is easy to recognize and manage. Ribavirin is contraindicated in patients with chronic anemia and a hemoglobin level below 10 gm/dL.

Apart from anemia, the only adverse event which was statistically significant more frequent in the Ribavirin group compared to the placebo group was pruritus. There appeared to be a non-statistically

significant trend towards a higher frequency of certain central nervous system events (e.g., depression, nervousness) in the Ribavirin group.

Ribavirin therapy was associated with a slight elevation of the serum uric acid level and of the platelet count. The size of these elevations was not clinically significant and there were no reports of gout attacks or any effects related to elevated platelet count. The effect on the serum uric acid level may relate to metabolism of Ribavirin to urates. The effect on the platelet count had been observed in animal toxicology studies and the significance of the finding is not known.

No other effects of treatment on laboratory parameters were identified. Apart from the one patient who withdrew from treatment due to anemia, there were no withdrawals due to laboratory abnormalities.

Ribavirin has no known drug interactions, although interactions with agents other than theophylline have not been studied. No long-term adverse effects or withdrawal effects have been identified. There is no known potential for abuse, and no experience for overdose. Thus Ribavirin can be used for long periods of time.

Therefore, according to one aspect of the invention, Applicants have developed a new use for ribavirin namely, the use of ribavirin as a hepato (liver) protecting agent (for example, when treating hepatitis C).

In this regard, while the administration of ribavirin does not eradicate the hepatitis C virus from the liver, its administration protects the liver, (as for example, determined from liver biopsies). In protecting the liver, the ribavirin prevents the condition of the liver from worsening and, in many cases, improves the condition of the liver. Thus, ribavirin protects the liver.

According to another aspect of the invention, a method of protecting the liver from viral diseases comprises administering an effective amount of ribavirin (for example, 1200 mg daily) to a patient in need of such protection (for example, a patient suffering from chronic hepatitis C) for a

prolonged period of time (for example, for in excess of one year) to protect the patient's liver.

According to another aspect of the invention, the use of ribavarin is provided in the manufacture a pharmaceutical composition for the use as a hepato (liver) protecting agent. The ribavirin may be used to manufacture dosage forms which can be administered in effective dosage amounts (for example, 1200 mg daily) to the patient whose liver is in need of protection (because the patient is for example, suffering from chronic hepatitis C). The pharmaceutical composition may comprise suitable excipients (such as fillers, diluents, flow enhancers). However, preferably each dosage form comprises ribavirin in excess of 70% (by weight) of the dosage amount of the active and excipients to ensure that the amount of ribavirin administered is maximized while minimizing the size of the dosage form so that the patient can take a minimum dosage size containing a maximum amount of ribavarin to ease patient compliance (who must take dosages every day). Preferably, the amount of ribavirin in the dosage exceeds 70% for example, the amount of ribavarin is 80% or more of the dosage amount of active and excipients (by weight) while ensuring the filling has the appropriate amount of excipients to ensure proper dispersion in the patient's system.

The invention does not just have application to patients infected with hepatitis C. The inventors also envisage application to the treatment of patients having other viruses which viruses affect the liver. Thus, the use ribavarin as a hepato (liver) protecting agent is not limited to patients suffering from hepatitis C.

Furthermore, because of Applicants' invention, a maintenance therapy can be provided which involves the use of ribavarin for maintenance of the condition of a patient's liver, even when the patient is being treated with other medicines.

An overview of clinical studies is provided hereinafter:

Adequate and well-controlled studies have shown that oral Ribavirin can produce clinically meaningful effects in patients with chronic hepatitis C, including normalization or reduction of ALT levels and improvement in liver histology.

Three placebo-controlled studies of Ribavirin in the treatment of chronic hepatitis C were conducted. These studies included 134 patients treated with Ribavirin and 97 patients who received placebo. There were also two uncontrolled Phase II studies including a total of 23 patients treated with Ribavirin. The primary response parameter was normalization or reduction of serum ALT levels. Response was also assessed in terms of elimination or reduction of serum HCV RNA levels, and improvement in liver histology as assessed by changes in Knodell scores.

In all of the controlled and uncontrolled studies, using the definitions of response specified in the protocols and analysis plans, Ribavirin was statistically significantly superior to placebo in normalizing and reducing ALT levels during treatment. In the integrated analyses based on all patients in the controlled studies, using a uniform definition of response including normalization of ALT at the end of treatment or a clinically meaningful level of partial response, 46% of Ribavirin patients were responders compared to 4% of placebo controls ($p < 0.001$). Patients generally responded after two to three months of treatment and the response was maintained as long as treatment was continued. There was no evidence of loss of ALT response with increasing duration of treatment. Following withdrawal of Ribavirin at the end of the active treatment phase, 11.5% of responders had a sustained response throughout the follow-up period.

Regarding improvement in liver histology, in each of the controlled studies there was a non-significant trend in favour of Ribavirin in the changes in total Knodell scores and many of the component scores. Analysis of the combined data by analysis of covariance using the baseline

Knodell score as covariate resulted in statistically significant differences in favour of Ribavirin for the total score and each of the component scores. Thus in the controlled studies, in comparing all Ribavirin-treated patients with placebo recipients, Ribavirin had a modest but real effect in improving liver histology. Within the Ribavirin group, comparison of ALT responders and non-responders revealed that ALT responders experienced a significantly greater improvement in liver histology as compared to ALT non-responders. The mean fall in total Knodell score was approximately two points for ALT responders as compared to one point for all Ribavirin-treated patients. A fall in total Knodell score of two points is generally considered by hepatologists to be clinically significant. There was thus a statistically significant positive correlation between ALT response and a clinically significant degree of improvement in liver histology.

In all studies, the primary end point was defined as a reduction in ALT level. In all studies a complete ALT response was defined as normalization of the ALT level at the end of treatment. A partial ALT response was defined as either a 50% or greater reduction at the end of treatment from the patient's baseline value, or a 50% or greater reduction to a level not higher than 1.5 times the upper limit of normal.

Table 1 (see page 15) displays the response rates in terms of improvement in liver histology. There were no statistically significant differences between the treatment groups in the changes in Knodell scores in any of the studies, although there were numerical trends in favour of Ribavirin. In study CT00/002 there was a difference in favour of Ribavirin in one of the secondary parameters (lymphoid aggregates, $p=0.05$).

In studies 92-001 and 91-DK-178, the treatment groups were compared with respect to the effect of the study medication on symptoms relevant to hepatitis. This could not be done in study CT00/002 because the case report form did not permit the systematic collection of symptom data.

In study 92-001, there was a statistically significant difference in favour of Ribavirin for decreased fatigue. At the end of treatment and at the end of the follow-up period, a higher proportion of Ribavirin patients showed some improvement from baseline in fatigue compared to placebo patients ($p=0.04$ for end of treatment and $p=0.006$ for end of follow-up). In this study there were no significant differences between the treatment groups for any other symptoms.

In study 91-DK-178, there were isolated significant differences between the treatment groups in individual symptoms at individual visits, some favouring the placebo group and some the Ribavirin group, but there were no overall trends favouring either treatment group.

Table 1. Comparison of Results of Controlled Studies - Liver Histology

Protoc 1	Protocol Definition of Response	Analysis Plan Definition of Response	Result
92-001	Comparison of treatment groups with respect to the changes from pre- to post-treatment in each patient's Knodell scores	Same	No significant difference between treatment groups
91-DK-178	Long-term response: Improvement in liver histopathology by "blinded ranking of all liver biopsies for the degree of current hepatic injury using the Wilcoxon rank sum test"	Comparison of treatment groups with respect to the changes from pre- to post-treatment in each patient's Knodell scores	No significant difference between treatment groups
CT00/002	Improvement in degree of inflammatory activity from pre- to post-treatment as assessed by Knodell scores	Comparison of treatment groups with respect to the changes from pre- to post-treatment in each patient's Knodell scores	No significant difference between treatment groups
		Pre- to post-treatment changes in other histological parameters thought to be relevant to hepatitis C	Reduction in lymphoid aggregates in Ribavirin group

Further analyses were performed in respect of the different studies. However, to make the results of these analyses more meaningful, the control studies data were combined to make the sample sizes larger.

Results of Integrated Analyses

a. Analysis of Response to Ribavirin According to the Relevant Effectiveness Criteria

1. ALT Response During Ribavirin Therapy

For the purposes of the integrated effectiveness analyses, the following definitions of ALT response were used:

Complete Response = return to within the normal range at the end of treatment.

Partial Response = 50% or greater reduction from the patient's baseline level to within 1.5 times the upper limit of normal at the end of treatment.

"Responder" = meets above definitions of either complete or partial response.

The definition of "responder" was determined by plotting the ALT values over time for the groups of patients fitting various definitions of response employed within each study. The data were fitted with a cubic spline smoothing function (Reinsch 1967). Three definitions of response were used:

- a. Complete response = ALT in normal range at end of treatment.
- b. Partial response(A) = 50% or greater reduction from the patient's baseline level to within 1.5 times the upper limit of normal at the end of treatment.

- c. Partial response(B) = 50% or greater reduction from the patient's baseline level at the end of treatment.

All other patients were considered non-responders. Plots were also constructed for Ribavirin-treated non-responders within each study and for all placebo patients (responders and non-responders) within each study.

The three curves for "complete response" demonstrated that this response was achieved after approximately one third of the treatment period and was maintained thereafter. The three curves for "partial response(A)" demonstrated a similar pattern of response. The three curves for "partial response(B)" demonstrated distinctly more variability of ALT levels during the treatment periods. The plots for Ribavirin-treated non-responders and the plots for placebo patients demonstrated, as expected, a dispersion of the data points which did not change in any recognizable pattern across the treatment and follow-up periods. It was decided that the "partial response(B)" definition was inappropriate for the purpose of the integrated effectiveness analyses. Due to the consistent pattern of response demonstrated by the "complete response" and "partial response(A)" definitions, and the fact that these definitions are clinically meaningful, it was decided that for the purpose of the integrated effectiveness analyses a "response" be defined as either "complete response" or "partial response(A)."

Table 2 displays the results for each study and for the combined database, using the above definition of ALT response. The proportions of responders in the two treatment groups were compared using either a Chi-square or Fisher's Exact test.

Table 2. Percent ALT Response Rates

Study	Ribavirin n/N (%)	Placebo n/N (%)	p Value
92-001	15/28 (53.6)	1/30 (3.3)	<0.001
91-DK-178	11/29 (37.9)	1/29 (3.4)	<0.001
CT00/002	32/70 (45.7)	2/36 (5.6)	<0.001
Combined database	58/127 (45.7)	4/95 (4.2)	<0.001
n = Number of patients with an ALT response (integrated definition) N = All patients treated (intent-to-treat population) minus those without valid non-missing observations.			

For the purpose of identifying the ALT value corresponding to the end of treatment, the last valid, non-missing observation, going back a maximum of two visits, was carried forward for those patients missing such a true value. This same policy was employed in two out of the three controlled studies (91-DK-178 and CT00/002). Nine patients in the Ribavirin group and two placebo patients did not have such a valid non-missing observation available.

The ALT response rates were consistent across the three controlled studies and ranged from 37.9 to 53.6%. When the data were combined the ALT response rate was 45.7%. In all instances, the ALT response rates for patients treated with Ribavirin were statistically significantly superior to the rates in patients treated with placebo. In the placebo group, ALT response rates were consistently low and ranged from 3.3 to 5.6% and 4.2% when the data were combined.

2. ALT Response in the Follow-Up Period

Table 3 summarizes the rates of sustained response in studies 92-001 and 91-DK-178 and in these two studies combined. The individual study analysis plan definitions of sustained response are used. A

sustained responder is essentially a patient with either normalization of ALT or a partial response at the end of treatment, who still meets either of these criteria throughout the follow-up period. It was not possible to provide this same analysis for study CT00/002 because too few patients had complete ALT data throughout the follow-up period.

Table 3. Percent ALT Sustained Response Rates - Protocol Definitions

Study	Ribavirin n/N (%)	Placebo n/N (%)
92-001	1/15 (6.7)	0/1 (0.0)
91-DK-178	2/11 (18.2)	0/1 (0.0)
Combined database	3/26 (11.5)	0/2 (0.0)
n = Number of patients with a sustained ALT response N = Number of patients with complete or partial response at the end of treatment (study analysis plan definitions)		

In the two studies analyzed, the sustained ALT response rates were 6.7 and 18.2% for Ribavirin-treated patients compared with 0% for patients receiving placebo.

Due to the low sample size and the very low number of placebo responders a statistical analysis was not performed.

Improvement in Knodell Scores

Within each of the three controlled studies, there was a consistent numerical trend in favour of Ribavirin in the changes in total scores and in many of the component scores. This same trend was thus apparent when the data from the three studies was combined. The trend applies not only to improvement of scores but also to worsening, indicating that even if no patients in either treatment group improve, then fewer patients in the Ribavirin group are worsening. This is an important observation considering that one objective of treatment is to prevent deterioration of a chronic and progressive condition. Analysis of the combined data by the CMH chi-square test does not reveal any statistically significant differences. Analysis of the combined data by analysis of variance

(as used in studies 92-001 and 91-DK-178) revealed a statistically significant difference in favour of Ribavirin for the total Knodell score but not for any of the component scores.

The liver histology data was examined further by analysis of covariance, using the baseline Knodell score as covariate. Regression analysis of the baseline Knodell scores versus the end of treatment scores for all Ribavirin-treated and placebo patients combined resulted in a slope of less than 1.0 but greater than zero. This indicated that the baseline Knodell score influenced the expectation of outcome of treatment, regardless of any difference between Ribavirin and placebo. Where the regression slope differs markedly from 1.0, analysis of covariance is a more appropriate test than analysis of variance (Fisher 1951). The result of the analysis of covariance is displayed in Table 4. The mean changes in the scores for Ribavirin-treated patients are only small, but due to small variances the differences from placebo are statistically significant. It is of interest to note that the only Knodell sub-score that does not improve is fibrosis, and that there is less deterioration in the Ribavirin group than in the placebo group.

Table 4. Comparison of Ribavirin and Placebo in Terms of Changes in Knodell Scores from Baseline to End of Treatment -- Analysis of Covariance Using Baseline Knodell Score as Covariate All Phase III Studies Combined

Knodell Component	Mean Change in Score from Baseline to End of Treatment		p Value
	Ribavirin N = 107	Placebo N = 78	
Periportal Activity and Necrosis	-0.40	-0.01	0.0004
Portal Inflammation	-0.30	-0.10	0.0206
Lobular Necrosis	-0.33	-0.13	0.0019
Fibrosis	+0.07	+0.25	0.0071
Total score	-1.11	-0.05	0.0001

Examination of Correlation Between ALT Response and Improvement in Knodell Scores

In each of the three controlled studies, Ribavirin was significantly more effective than placebo in normalizing and reducing ALT levels. (An elevated serum ALT level is a biochemical indicator of hepatic inflammation.) Was there also a correlation between response to Ribavirin therapy in terms of normalization or reduction of ALT level within individual patients and by an improvement in liver histology as determined by Knodell scores. We found that there was indeed a consistent trend towards a positive relationship between ALT response and improvement in Knodell scores when both parameters are treated in a categorical manner. In the combined database, this trend was statistically significant for the Total Knodell score ($p = 0.008$), Fibrosis ($p = 0.014$), and Portal Inflammation ($p = 0.022$) using the Cochran-Mantel-Haenszel (CMH) chi-square test (Table 5 through Table 7).

Table 5. Knodell Response Status by Controlled Studies – Total by ALT Response

		Responder		Non-responder			
Protocol	Response	n	%	n	%	P-Value 1	
92-001	Improved	7	46.7	4	33.3	0.099	
	Unchanged	7	46.7	3	25.0		
	Worsened	1	6.7	5	41.7		
91-DK-178	Improved	10	90.9	7	38.9	0.021	*
	Unchanged	1	9.1	5	27.8		
	Worsened	0	0.00	6	33.3		
CT00/002	Improved	11	42.3	12	48.0	0.171	
	Unchanged	11	42.3	5	20.0		
	Worsened	4	15.4	8	32.0		
Integrated	Improved	28	53.8	23	41.8	0.008	*
	Unchanged	19	36.5	13	23.6		
	Worsened	5	9.6	19	34.5		

N = Number of patients in study
 n - Number of patients in response category
 % = (n/N)*100
 1 Cochran-Mantel-Haenszel Statistic
 * P<0.05

		Responder		Non-responder			
Protocol	Response	n	%	n	%	P-Value 1	
92-001	Improved	2	13.3	1	0.0	0.434	
	Unchanged	12	80.0	11	91.7		
	Worsened	1	6.7	1	8.3		
91-DK-178	Improved	5	45.5	2	11.1	0.119	
	Unchanged	4	36.4	11	61.1		
	Worsened	2	18.2	5	27.8		
CT00/002	Improved	6	23.1	1	4.0	0.120	
	Unchanged	18	69.2	20	80.0		
	Worsened	2	7.7	4	16.0		
Integrated	Improved	13	25.0	3	5.5	0.014	*
	Unchanged	34	65.4	42	76.4		
	Worsened	5	9.6	10	18.2		

N = Number of patients in study
 n - Number of patients in response category
 % = (n/N)*100
 1 Cochran-Mantel-Haenszel Statistic
 * P<0.05

Table 7. Knodell Response Status by Controlled Studies -- Portal Inflammation by ALT Response

		Responder		Non-responder			
Protocol	Response	n	%	n	%	P-Value 1	
92-001	Improved	5	33.3	3	25.0	0.220	
	Unchanged	9	60.0	5	41.7		
	Worsened	1	6.7	4	33.3		
91-DK-178	Improved	5	45.5	4	22.2	0.227	
	Unchanged	6	54.5	11	61.1		
	Worsened	0	0.0	3	16.7		
CT00/002	Improved	5	19.2	6	24.0	0.159	
	Unchanged	21	80.8	16	64.0		
	Worsened	0	0.0	3	12.0		
Integrated	Improved	15	28.8	13	23.6	0.022	*
	Unchanged	36	69.2	32	58.2		
	Worsened	1	1.9	10	18.2		

N = Number of patients in study
n - Number of patients in response category
% = (n/N)*100
1 Cochran-Mantel-Haenszel Statistic
* P<0.05

The relationship between ALT response and improvement in liver histology was studied further in order to quantify the improvement in liver histology in patients responding to Ribavirin, and to determine if there was a subgroup of patients who derive a more substantial clinical benefit from treatment with Ribavirin. In each of the three controlled studies, Ribavirin-treated ALT responders and non-responders were compared in terms of the mean changes in total Knodell scores over the course of treatment. This analysis, displayed in Table 8 thus quantifies the directional changes displayed in Table 5.

It can be seen that in each study there was a correlation between ALT response and improvement in liver histology, in that ALT response was associated with a greater improvement in liver histology as compared to ALT non-responders. This effect was particularly striking in study 91-DK-178, where there was a mean Knodell score reduction of 4.09 in ALT responders as compared to 0.17 in ALT non-responders. A regression model was employed to examine the relationship between ALT response and Knodell score changes. This revealed that in all three studies ALT Response was a significant predictor of improvement in liver histology. Thus, ALT normalization or reduction correlates with improvement in liver histology in patients with hepatitis C treated with Ribavirin, and patients who achieve an ALT response are likely to derive a substantial clinical benefit. In patients treated with Ribavirin who do not achieve an ALT response, there does not appear to be any clinical benefit in comparison to patients who received placebo.

Table 8.

Study	CT00/002	92-001	91-DK-178	Combined Database
Duration of Treatment (Weeks)	24	36	48	
Mean Knodell Change (Range) in ALT Responders*	-1.23 (-7,4) n = 26	-1.47 (-8,2) n = 15	-4.09 (-9,0) n = 11	-1.90 (-9,4) n = 52
Mean Knodell Change (Range) in ALT Non-responders	-0.96 (-9,4) n = 25	+0.58 (-3,6) n = 12	-0.17 (-6,7) n = 18	-0.36 (-9,7) n = 55
P Value **	0.004	0.0001	0.002	0.0001
Mean Knodell Change (Range) all Ribavirin Patients	-1.10 (-9,4) n = 51	-0.56 (-8,6) n = 27	-1.65 (-9,7) n = 29	-1.11 (-9,7) n = 107
Mean Knodell Change (Range) All Placebo Patients	-0.09 (-4,4) n = 23	+0.44 (-3,5) n = 27	-0.52 (-8,4) n = 27	-0.51 (-8,5) n = 77
P Value	NS	NS	NS	0.01
<p>* ALT response was defined as normalization at the end of treatment or reduction of 50% or more from baseline to within 1.5 times the upper limit of normal at the end of treatment.</p> <p>** Regression analysis.</p>				

Thus, in summary, the phase III program on Ribavirin in chronic hepatitis C consisted of three randomized, double-blind, placebo-controlled, parallel group studies. A total of 134 patients were randomized to

receive Ribavirin and 97 to receive placebo. Response to treatment was assessed using three parameters:

1. Reduction or normalization of the ALT level (elevation of ALT is a biochemical marker of hepatic inflammation).
2. Improvement in liver histology as evidenced by a reduction in the Knodell score (the Knodell scoring system quantifies the degree of liver damage by assigning scores to various relevant microscopic characteristics and summing these sub-scores to give a total score).
3. Elimination of hepatitis C virus from the blood, or a reduction in the amount of virus present.

Of the 134 patients in the phase III studies, there were 101 with complete data on ALT levels, Knodell scores and virus levels. Among these 101 patients, there were 24 patients who met the criteria for an optimal clinical response to Ribavirin therapy. These criteria are:

- (a) Normalization or clinically significant reduction of the ALT level, and reduction in total Knodell score of two or more points.

For these 24 patients, the clinical response was obtained without an accompanying reduction in the virus level in the blood. The table below summarizes the data on ALT levels and Knodell scores for the 24 responding patients as compared to the remaining 77 patients who demonstrated lesser degrees of response.

	Responders N=24	Non-Responders N=77
Mean baseline ALT (range) U/L	142.5 (52-269)	176.9 (35-629)
Mean end-of- treatment ALT (range)* U/L	36.8 (21-62)	91.7 (13-286)
Mean Knodell score reduction (range)	4.1 (2-9)	0.15 (-7 to+9)

* upper limit or normal is 40 U/L

As many changes can be made to the examples without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS BEING CLAIMED ARE AS FOLLOWS:

1. Use of ribavirin as a hepato (liver) protecting agent.
2. Use of a pharmaceutical composition containing ribavirin and pharmaceutically acceptable excipients as a hepato (liver) protecting agent.
3. Use of a pharmaceutical composition containing ribavirin and pharmaceutically acceptable excipients as a hepato (liver) protecting agent wherein the amount of ribavirin exceeds 70% by weight of the active and excipients in the pharmaceutical composition.
4. The use of Claim 3 wherein the amount of ribavirin is about 80% by weight of the active and excipients in the pharmaceutical composition.
5. The use of ribavirin in an amount equal to or exceeding 1200 mg daily for a period of at least a year as a hepato (liver) protecting agent.
6. The use of Claim 1, 2, 3, 4 or 5 wherein the ribavirin is substituted by a form of ribavirin in an amount equivalent to the amount of ribavirin.
7. The use of the pharmaceutical composition of Claim 3 or 4 for a period of at least about a year.

8. The use of the pharmaceutical composition of Claim 3, 4 or 7 wherein the ribavirin is in a dosage amount of at least about 1200 mg daily.

9. A pharmaceutical composition comprising ribavirin and pharmaceutically acceptable excipients wherein the amount of ribavirin exceeds 70% by weight of the active and excipients in the pharmaceutical composition.

10. A new use for ribavirin namely, the use of ribavirin as a hepato (liver) protecting agent (for example, when treating hepatitis C).

11. The use of Claim 10 wherein, while the administration of ribavirin does not eradicate the hepatitis C virus from the liver, its administration protects the liver, protecting the liver, wherein the ribavirin prevents the condition of the liver from worsening and, in many cases, improves the condition of the liver.

12. A method of protecting the liver from viral diseases comprising administering an effective amount of ribavirin (for example, 1200 mg daily) to a patient in need of such protection (for example, a patient suffering from chronic hepatitis C) for a prolonged period of time (for example, for in excess of one year) to protect the patient's liver.

13. The use of ribavirin in the manufacture of a pharmaceutical composition for the use as a hepato (liver) protecting agent.

14. The use of Claim 13 wherein the ribavirin may be used to manufacture dosage forms which can be administered in effective dosage amounts (for example, 1200 mg daily) to the patient whose liver is in need of protection (because the patient is for example, suffering from chronic hepatitis C).
15. The pharmaceutical composition of Claim 9 comprising suitable excipients (such as fillers, diluents, flow enhancers).
16. The pharmaceutical composition of Claim 15 wherein each dosage form comprises ribavirin in excess of 70% (by weight) of the dosage amount of the active and excipients to ensure that the amount of ribavirin administered is maximized while minimizing the size of the dosage form so that the patient can take a minimum dosage size containing a maximum amount of ribavirin to ease patient compliance.
17. A maintenance therapy involving the use of ribavirin for maintenance of the condition of a patient's liver, even when the patient is being treated with other medicines.

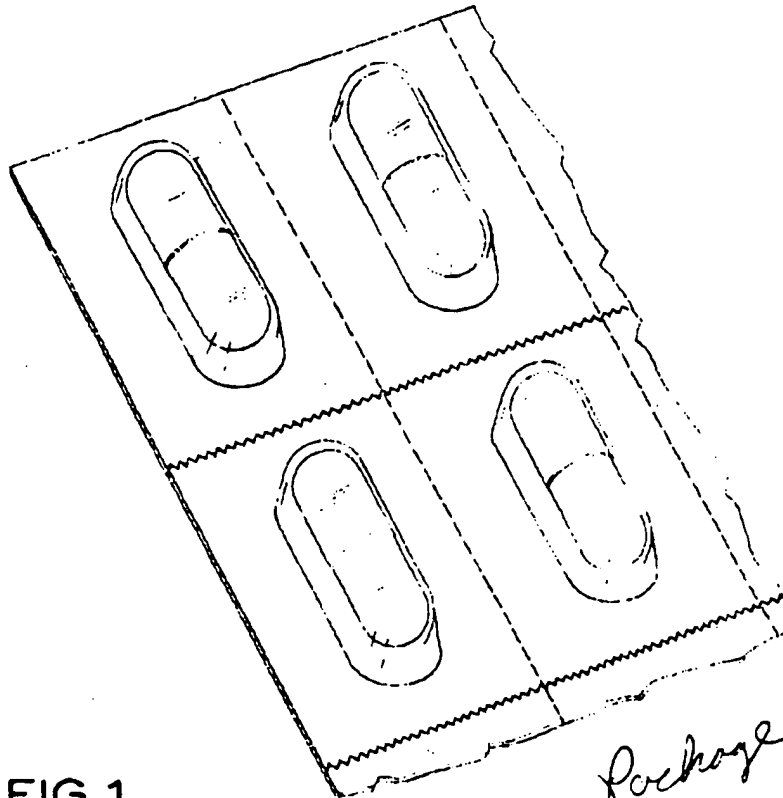


FIG.1.

*Plastic Package
Close up*

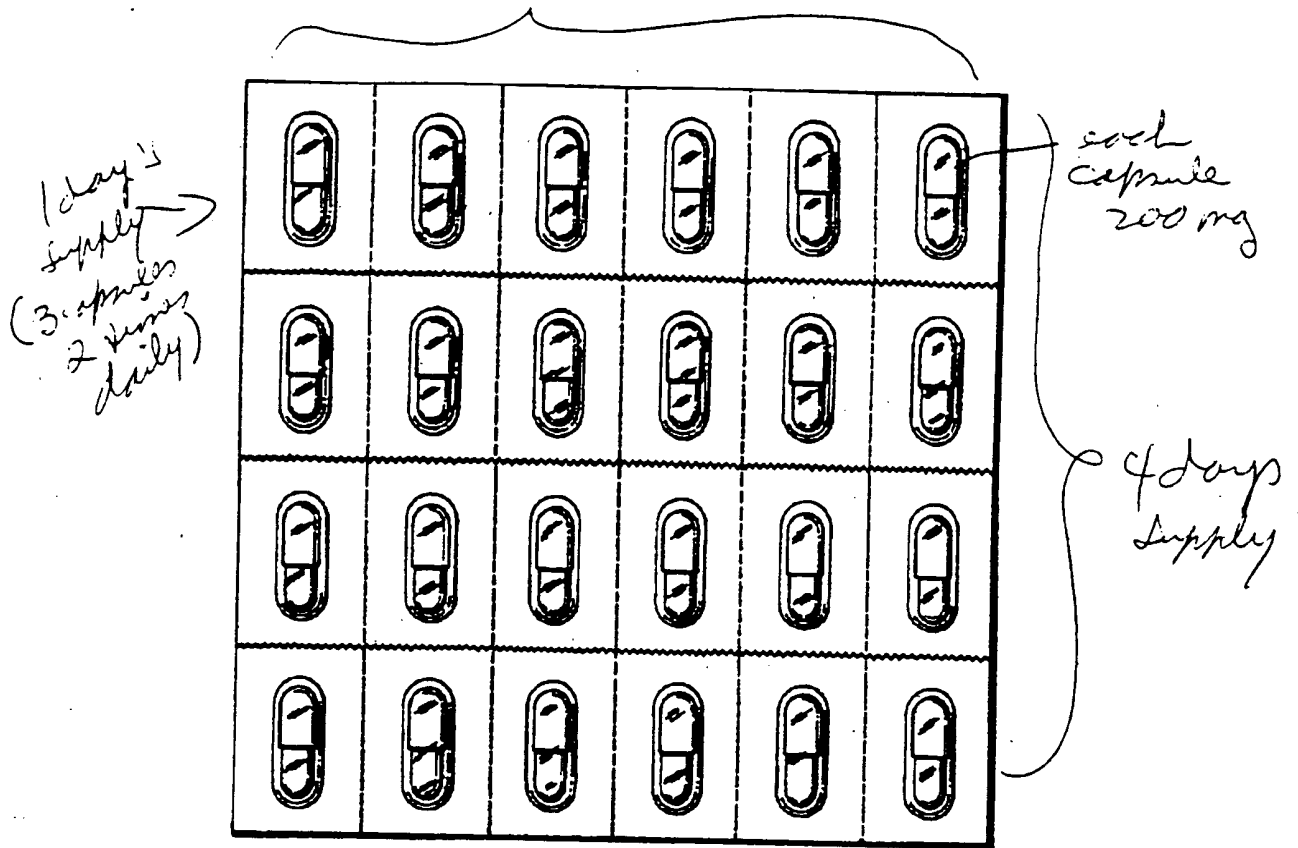


FIG.2.

213,669

7 days supply
of capsules of 200 mg
of Ribavirin

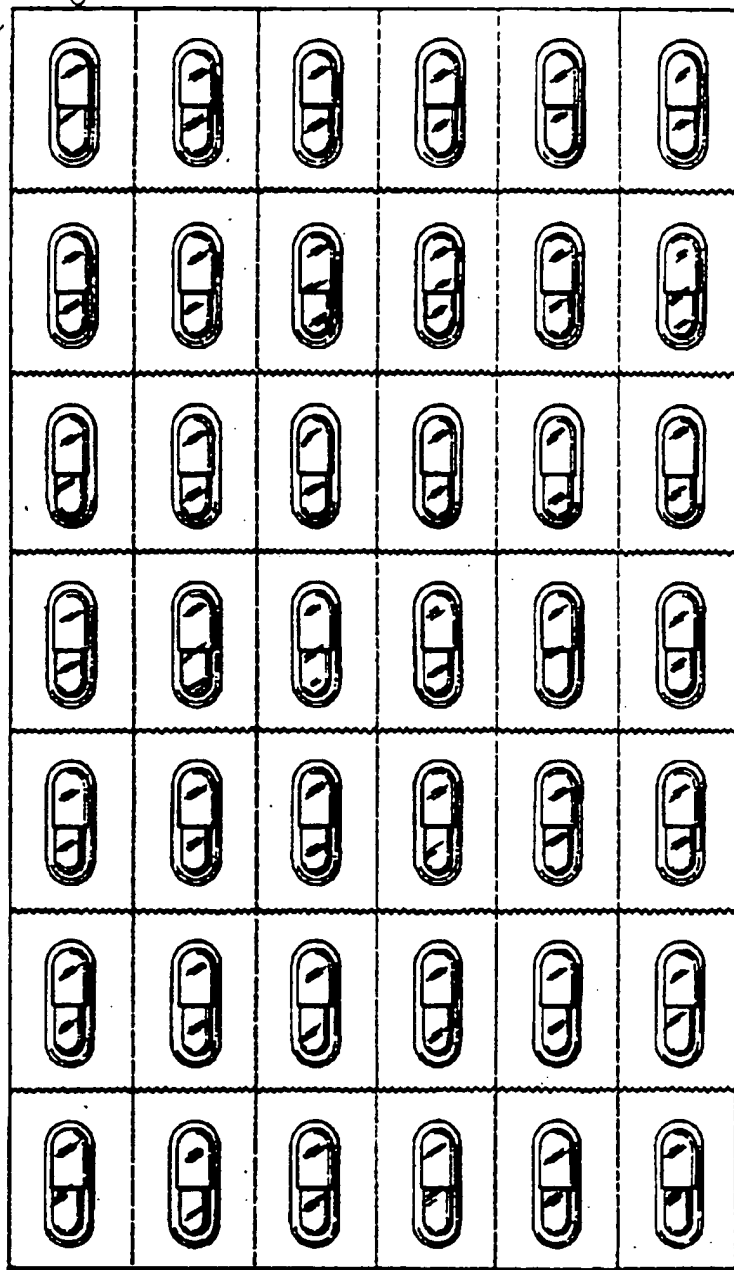
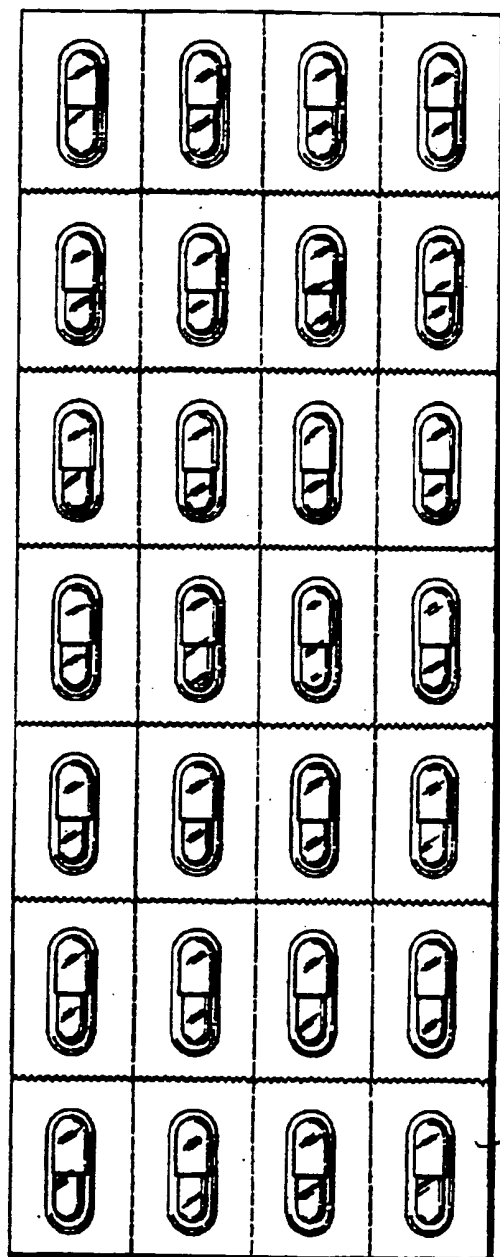


FIG.3.

2135669

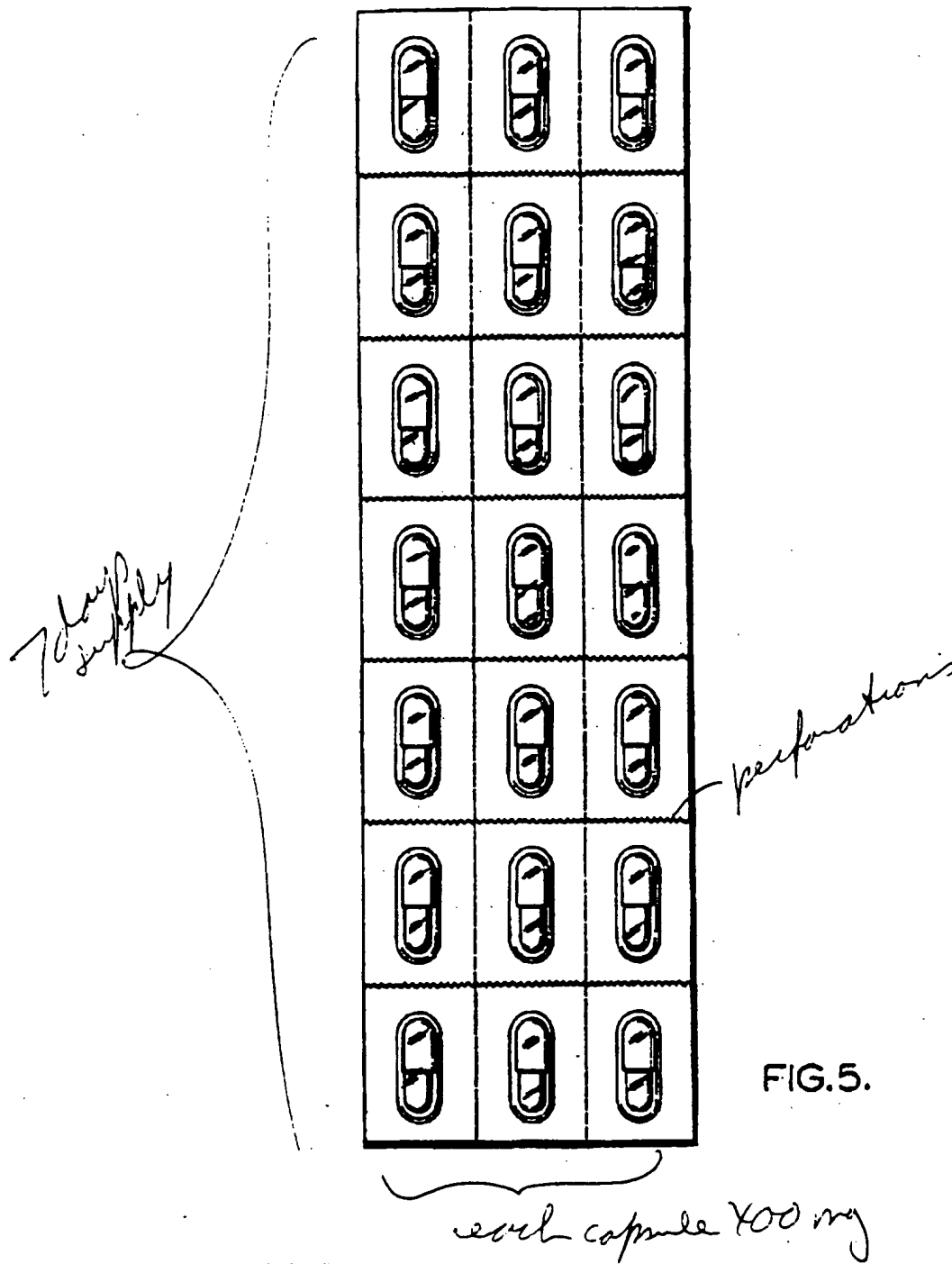


7 days
Supply

300 mg capsules
x4

FIG.4.

2135669



2135669

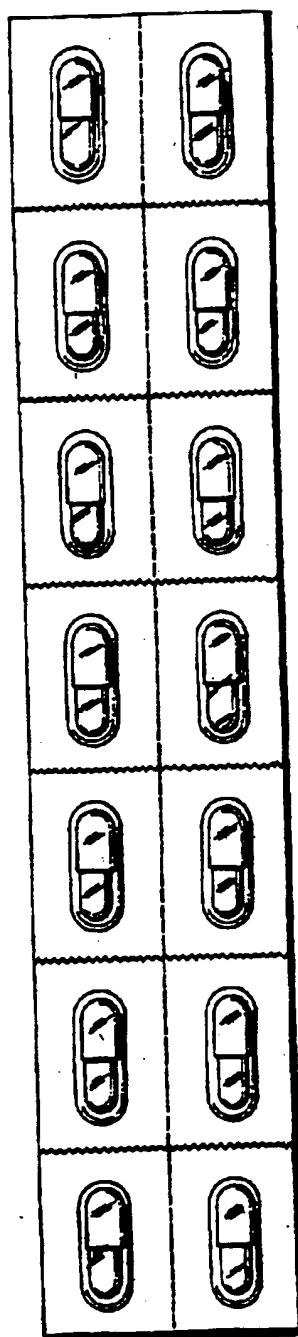


FIG.6.

7 day supply

*600 mg
each
capsule*